REMARKS

Claim Amendments and New Claims 23-34

Support for new Claims 23-32 is found in the specification, for example, at page 2, lines 11-12 and lines 21-22, which incorporate by reference the entire contents of United States Patent Nos. 5,500,412 and 5,352,664; and at page 10, lines 3-8. Support for the claim amendments are found in the specification, for example, at page 2, lines 23-25; page 6, lines 3-13; and page 10, lines 14-18.

No new matter is added by the new claims or by the claim amendments.

Item 1: Restriction Requirement

Applicant thanks the Examiner for withdrawing the restriction requirement.

Item 2: Information Disclosure Statement

A Supplemental Information Disclosure Statement (IDS) is being filed concurrently herewith. Entry and consideration of the IDS are respectfully requested.

Items 3 to 5: Rejection of Claims 1, 6-16, 21 and 22 Under 35 U.S.C. § 112, First Paragraph

Claims 1, 6-16, 21 and 22 have been rejected under 35 U.S.C. § 112, first paragraph, because, in the Examiner's assessment, the specification does not reasonably provide enablement for all angiogenic thrombin derivative peptides. The Examiner states that the amount of guidance presented in the specification is limited to angiogenic thrombin derivative peptides having both a thrombin receptor binding domain and a serine esterase conserved sequence (Paper No. 03022004, at page 4, lines 9-12).

Applicant disagrees with the Examiner's conclusion that the specification does not enable angiogenic thrombin derivative peptides as set forth in original Claims 1, 6-16, 21 and 22. However, in an effort to advance prosecution in the subject application and without acquiescing to the Examiner's rejection or waiving the right to prosecute the full scope of the original claims in the future, Claim 11 has been cancelled and Claims 1, 6-10, 12-16, 21 and 22 have been

amended to recite that the angiogenic thrombin derivative peptides comprise a thrombin binding domain and a serine esterase conserved sequence.

Claims 1, 6-16, 21 and 22 have also been rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The Examiner alleges that the rejected claims "read on a method using literally any peptide with angiogenic activity that has fewer amino acids than thrombin, or less than 308 amino acids" (Paper No. 03022004, at page 5, last paragraph). The Examiner also alleges that "[t]he only disclosure is those angiogenic peptides having at least 23 amino acids but no more than 307 amino acids comprising a polypeptide derivative of thrombin which has a thrombin receptor binding domain with a serine esterase conserved sequence" and that "[n]o structure-to-function relationship is disclosed other than the combination of the thrombin receptor binding domain and a serine esterase conserved sequence" (Paper No. 03022004, at page 5, last paragraph). Applicant respectfully disagrees with this assessment.

Applicant provides detailed characteristics for the angiogenic thrombin derivative peptides recited in the rejected claims (i.e., Claims 1, 6-16, 21 and 22). In particular, Applicant's specification teaches that angiogenic thrombin derivative peptides are compounds which can be employed to induce angiogenic proliferation and migration of endothelial cells resulting in formation of new capillaries and collateral vessels to help restore function to damaged or ischemic heart tissue (see specification, e.g., page 4, lines 22-24). Angiogenic thrombin derivative peptides possess a thrombin receptor binding domain and a serine esterase conserved sequence (see specification, e.g., page 6, lines 3-13). The thrombin receptor binding domain includes a segment of the polypeptide that is capable of selectively binding to the high-affinity thrombin receptor and which includes a sequence of amino acids homologous to a tripeptide cell binding domain of fibronectin (see specification, e.g., page 6, lines 3-13).

Specific examples of angiogenic thrombin derivative peptides are provided in the specification (see, e.g., page 6, lines 21-28). Other thrombin derivative peptides are disclosed in U.S. Patent No. 5,352,664 and U.S. Patent No. 5,500,412, which are incorporated into the subject application by reference (see specification, e.g., page 2, lines 11-12 and lines 21-22). Thus, a person skilled in the art would recognize from the disclosed characteristics that Applicant was in

possession of the claimed genus of angiogenic thrombin derivative peptides at the time the subject application was filed.

Reconsideration and withdrawal of the rejection of Claims 1, 6-10, 12-16, 21 and 22 are respectfully requested.

Items 6 and 7: Rejection of Claims 1-7, 10-11 and 22 Under 35 U.S.C. § 103(a)

Claims 1-7, 10-11 and 22 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Malinda *et al.* (U.S. Patent No. 6,197,751 B1) in view of Unger *et al.* (U.S. Patent No. 5,244,460) and Carney *et al.* (U.S. Patent No. 5,352,664). In support of the rejection, the Examiner alleges that it would have been obvious to one of ordinary skill in the art "to use the peptides of Carney et al. ('644) as angiogenic agents in the method of Malinda et al. with the expectation of beneficial results" (Paper No. 03022004, at page 7, second paragraph). The Examiner urges that "[m]otivation is provided by Unger et al. who disclose other angiogenic agents other than thymosin α1", which would have led one of ordinary skill "to expect that any angiogenic agent would work to promote cardiac cell growth and revascularization in accordance with the teachings of Malinda et al." (Paper No. 03022004, at page 7, second paragraph). Applicant respectfully disagrees that Claims 1-7, 10-11 and 22 are obvious in view of the cited references.

Claim 11 has been cancelled. Claims 1-7 are directed to methods for promoting cardiac tissue repair; Claim 10 is directed to a method of stimulating revascularization of cardiac tissue; and Claim 22 is directed to a method of inhibiting vascular occlusion. The methods of Claims 1-7, 10 and 22, as amended, comprise administering a therapeutically effective amount of an angiogenic thrombin derivative peptide which has angiogenic activity and comprises a thrombin binding domain and a serine esterase conserved sequence.

Unger *et al.* would not have led one of ordinary skill in the art "to expect that *any* angiogenic agent would work to promote cardiac cell growth and revascularization in accordance with the teachings of Malinda et al.".

First, in the Background section, at Column 3, lines 31-36, Unger *et al.* state that:

> There is ***no*** technology in existence at the present time that can foster the in vivo growth of new blood vessels in the heart, thereby improving cardiac blood flow. That is why the somewhat unsatisfactory procedures described above are still necessary to improve cardiac blood flow.

Unger *et al.* note that one of these "unsatisfactory procedures" is a "one-time treatment" with FGF immediately following a myocardial infarction (injections are given during one 24 hour period of time) (Col. 2, ll. 45-48).

At Column 3, lines 37-35, Unger *et al.* express additional skepticism, stating that:

> During the last six years, a number of proteins have been characterized that promote the growth of blood vessels in vitro. Despite their great promise in the treatment of cardiovascular disease, ***none*** have been successfully utilized in vivo to date. Moreover, to the present date, there has been ***no*** publication of any data directed to using any of these proteins in vivo to generate any blood vessels in mature tissue, i.e., in non-embryonic tissue.

Further skepticism is highlighted at Column 3, lines 47-57, where Unger *et al.* state that:

> As stated above, polypeptides, to date, have not been successively used to promote the growth of blood vessels in the heart, to regenerate vessels in a damaged or nearby area in a heart, or over a period of time to increase cardiac blood flow in a damaged area. The focus of the prior art has been upon the prevention of damage immediately following arterial blockage in the heart or brain. Moreover, there is no method in the prior art to provide these results or any directional details or discussion relating to a suitable dosage for accomplishing regeneration of new cardiac blood vessels.

Unger *et al.* then state in the Summary of the Invention section, at Column 4, lines 6-12, that:

> It is an object of the present invention to provide a procedure or method by which peptides may be made operable in vivo to promote new cardiac blood vessel growth in mature cardiac tissue, when such peptides have been characterized or shown to promote the growth of blood vessels in vitro or in embryonic tissue.

At Column 4, lines 18-34, Unger *et al.* teach that such a method "to facilitate in a damaged heart or a heart in need of improved circulation the growth of cardiac blood vessels while reducing the risk of undesired vascularization in other areas of the body" comprises directly injecting a growth promoting peptide into the heart via a catheter and "repeating

periodically on subsequent days" injection of the growth factor via the catheter. At Column 5, lines 1-7, Unger *et al.* define the phrase "repeating periodically on subsequent days" to mean:

> as continuing the step of injecting the peptide into the heart at more than one time on the same day, if necessary, and on additional designated days. The is significantly more than, and substantially different than just a one-day, single- or multiple-shot treatment in or around the time of a heart attack, which one-day injections are then not repeated.

In Examples 1 and 2, Unger *et al.* exemplify their method employing daily injections of two growth factors, VEGF and FGF (or fragments thereof), directly into the heart via a catheter.

Second, Malinda *et al.* is directed primarily towards wound healing using thymosin α1 (Tα1) peptide. Treatment of cardiac tissue damage using the Tα1 peptide is one of many treatments described by Malinda *et al.* In this particular treatment, it is said that the Tα1 peptide can induce angiogenesis in a tissue and stimulate collateral circulation in cardiac tissue affected by coronary occlusion, thereby restoring blood flow to ischemic tissues. See Col. 16, ll. 28-36. However, Malinda *et al.* do not provide any data to show that the Tα1 peptide has been used successfully to promote the growth of blood vessels in the heart, to regenerate vessels in a damaged or nearby area in a heart, or over a period of time to increase cardiac blood flow in a damaged area.

Thus, given the skepticism highlighted by Unger *et al.* and the absence of data in the prior art, one of ordinary skill in the art would not have been led to reasonably expect that any angiogenic agent would work to promote cardiac cell growth and revascularization in accordance with the teachings of Malinda *et al.*

Moreover, none of the cited references, either alone or in combination, teaches or suggests, with a reasonable expectation of success, that an angiogenic thrombin derivative peptide comprising a thrombin binding domain and a serine esterase conserved sequence can be used to promote cardiac tissue repair, stimulate revascularization of cardiac tissue or inhibit vascular occlusion.

Malinda *et al.* teach that the Tα1 peptide is a 28 amino acid peptide which results from cleavage of the N-terminal region of pro-thymosin α1 (Col. 8, ll. 50-52). The amino acid sequence for this 28 amino acid peptide is reported to be SDAAVDTSSEITTKDLKEKKEVVEEAE N (see Malinda *et al.*, *J. Immunology*, 160:1001-

1006 (1998); copy attached hereto as the Exhibit). The Tα1 peptide is not known to be a thrombin derivative peptide. Importantly, it is evident from the amino acid sequence for the Tα1 peptide that the Tα1 peptide does not comprise a thrombin binding domain or a serine esterase conserved sequence and therefore, the Tα1 peptide is unrelated to the angiogenic thrombin derivative peptides recited in Applicant's claims. Since the Tα1 peptide is not based on a thrombin sequence, one of ordinary skill in the art would not have been able to predict which thrombin fragments would have angiogenic activity, based on the teachings of Malinda *et al.*

As discussed above, Unger *et al.* teach a method in which a *growth promoting peptide* is directly injected via a catheter into a damaged heart or a heart in need of improved circulation to facilitate in the heart the growth of cardiac blood vessels (Col. 4, ll. 18-34). Unger *et al.* teach that growth promoting peptides that can be administered are epidermal growth factor, acidic fibroblast growth factor, basic fibroblast growth factor and vascular endothelial cell growth factor (Col. 5, ll. 45-49), as well as peptides "shown to have similar tissue growth stimulating functionality, either in vitro or in embryonic tissue" (Col. 5, ll. 49-53). Importantly, Unger *et al.* do not teach or suggest any peptides "shown to have similar tissue growth stimulating functionality, either in vitro or in embryonic tissue" other than the specific growth promoting peptides listed above. None of the specific growth promoting peptides disclosed by Unger *et al.* are considered to be thrombin derivative peptides. None of the specific growth promoting peptides disclosed by Unger *et al.* comprise a thrombin binding domain and serine esterase conserved sequence. Since the specific growth promoting peptides disclosed by Unger *et al.* are not based on a thrombin sequence, one of ordinary skill in the art would not have been able to predict which thrombin fragments would have angiogenic activity, based on the teachings of Unger *et al.* As such, Unger *et al.* do not cure the deficiencies of the Malinda *et al.* patent.

Carney *et al.* teach thrombin derivative peptides. Carney *et al.* do not teach or suggest the use of the thrombin peptide derivatives for promoting cardiac tissue repair, for stimulating revascularization of cardiac tissue, for stimulating vascular endothelial cell proliferation, for inhibiting vascular occlusion or for inhibiting restenosis. As such, Carney *et al.* do not teach or suggest the use of the thrombin derivative peptides in the methods of Claims 1-7, 10-11 and 22. Accordingly, Carney *et al.* do not cure the deficiencies of the Malinda *et al.* and Unger *et al.* patents.

Accordingly, none of the cited references, alone or in combination, would have suggested the methods of Claims 1-7, 10 and 22 to one of ordinary skill in the art at the time of the invention, with a reasonable expectation of success. More specifically, none of the cited references, either alone or in combination, would have suggested that an angiogenic thrombin derivative peptide comprising a thrombin binding domain and a serine esterase conserved sequence could be used to successfully promote cardiac tissue repair, stimulate revascularization of cardiac tissue, stimulate vascular endothelial cell proliferation or inhibit vascular occlusion. In fact, prior to Applicant's results described in the subject application (see Examples 3 and 4), one of ordinary skill in the art would not have reasonably expected that angiogenic thrombin derivative peptide comprising a thrombin binding domain and serine esterase conserved sequence can successfully promote formation of new blood vessels to help restore cardiac function to damaged or ischemic heart tissue.

Reconsideration and withdrawal of this rejection of Claims 1-7, 10 and 22 under 35 U.S.C. § 103(a) are respectfully requested.

Item 8: Rejection of Claims 8 and 9 Under 35 U.S.C. § 103(a)

Claims 8 and 9 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Malinda *et al.* (U.S. Patent No. 6,197,751 B1) in view of Unger *et al.* (U.S. Patent No. 5,244,460) and Carney *et al.* (U.S. Patent No. 5,352,664) and further in view of Thim *et al.* (U.S. Patent No. 5,912,229). Malinda *et al.*, Unger *et al.* and Carney *et al.* are applied as discussed above. In support of the rejection, the Examiner alleges that it would have been obvious to one of ordinary skill in the art "to place the peptides of Carney et al. ('644) into sustained release microcapsules [of Thim et al.] for administration according to the method of Malinda et al. with the expectation of attaining the well-known benefits of sustained release of medicine" (Paper No. 03022004, at page 7, last paragraph). Applicant respectfully disagrees that Claims 8-9 are obvious in view of the cited references.

Applicant notes that Claims 8 and 9 ultimately depend from Claim 1. For the reasons set forth above, Unger *et al.* would not have led one of ordinary skill in the art "to expect that *any* angiogenic agent would work to promote cardiac cell growth and revascularization in accordance with the teachings of Malinda et al.". Additionally, Malinda *et al.*, Unger *et al.* and Carney *et al.*,

either alone or in combination, do not teach or suggest that an angiogenic thrombin derivative peptide comprising a thrombin binding domain and serine esterase conserved sequence can be used to promote cardiac tissue repair with a reasonable expectation of success.

Thim *et al.* teach the use of appetite-suppressing peptides, particularly the GLP-2 peptide, for treatment of obesity and type II diabetes. Thim *et al.* teach that the appetite-suppressing peptides, such as the GLP-2 peptide, may be formulated as sustained release formulations, particularly as microcapsules or microparticles, wherein the appetite-suppressing peptides are encapsulated by or dispersed in a biodegradable polymer such as polylactic acid, polyglycolic acid or a lactic acid/glycolic acid copolymer (Col. 10, ll. 10-17). However, Thim *et al.* do not provide any data to show that appetite-suppressing peptides, such as GLP-2 have been used successfully to promote the growth of blood vessels in the heart, to regenerate vessels in a damaged or nearby area in a heart, or over a period of time to increase cardiac blood flow in a damaged area. Thus, given the skepticism highlighted by Unger *et al.* and the absence of data in the prior art, one of ordinary skill in the art would not have been led to reasonably expect that any angiogenic agent would work to promote cardiac cell growth and revascularization in accordance with the teachings of Malinda *et al.*

Moreover, Thim *et al.* teach that the appetite-suppressing peptides have the following amino acid sequence: $X^1HX^2DGSFSDEMNTX^3LDX^4LAX^5X^6DFINWLX^7X^8TKITDX^9$, wherein X^1 is NH_2, DFPEEVAIVEELGRR, DFPEEVTIVEELGRR, DFPEEVNIVEELRRR, or a fragment thereof; X^2 is Ala or Gly; X^3 is Ile or Val; X^4 is Asn, Ser or His; X^5 is Ala or Thr; X^6 is Arg or Lys; X^7 is Ile or Leu; X^8 is Gln or His; or X^9 is OH, Lys, Arg, Arg-Lys, Lys-Arg, Arg-Arg or Lys-Lys (Col. 3, ll. 4-24). These appetite-suppressing peptides are not known to be thrombin derivative peptides. Importantly, it is evident from the amino acid sequence for the appetite-suppressing peptides that these peptides do not comprise a thrombin binding domain and a serine esterase conserved sequence and therefore, the appetite-suppressing peptides are unrelated to the angiogenic thrombin derivative peptides recited in Applicant's claims. Since the appetite-suppressing peptides are not based on a thrombin sequence, one of ordinary skill in the art would not have been able to predict which thrombin fragments would have angiogenic activity, based on the teachings of Thim *et al.* As such, Thim *et al.* do not teach or suggest the use of the

thrombin derivative peptides in the methods of Claims 8 and 9. Accordingly, Thim *et al.* do not cure the deficiencies of the Malinda *et al.*, Unger *et al.* and Carney *et al.* patents.

Accordingly, none of the cited references, alone or in combination, would have suggested the methods of Claims 8 and 9 to one of ordinary skill in the art at the time of the invention, with a reasonable expectation of success. In particular, none of the cited references, either alone or in combination, would have suggested that an angiogenic thrombin derivative peptide comprising a thrombin binding domain and a serine esterase conserved sequence could be used to successfully promote cardiac tissue repair.

Reconsideration and withdrawal of this rejection of Claims 8 and 9 under 35 U.S.C. § 103(a) are respectfully requested.

Item 9: Rejection of Claims 12, 14 and 16-21 Under 35 U.S.C. § 103(a)

Claims 12, 14 and 16-21 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Malinda *et al.* (U.S. Patent No. 6,197,751 B1) in view of Unger *et al.* (U.S. Patent No. 5,244,460) and Carney *et al.* (U.S. Patent No. 5,352,664) and further in view of Saadat *et al.* (U.S. Patent No. 6,363,938 B2). Malinda *et al.*, Unger *et al.* and Carney *et al.* are applied as discussed above. In support of the rejection, the Examiner alleges that it would have been obvious to one of ordinary skill in the art "to coat stents with the peptides of Carney et al. ('644) as the bioactive agent when practicing the method of Saadat et al. with the expectation of achieving the beneficial results taught by Carney et al. ('644)" (Paper No. 03022004, at page 8, last paragraph). The Examiner also alleges that since Saadat *et al.* "discuss stenosis and the action of the angiogenic agent", one of ordinary skill in the art "would immediately realize that, since the reason for use of the stent in the first place is to relieve stenosis then use of the angiogenic agent would by definition inhibit restenosis in the patient" (Paper No. 03022004, at page 8, last paragraph). Applicant respectfully disagrees that Claims 12, 14 and 16-21 are obvious in view of the cited references.

Claims 12, 14 and 16-20 are directed to a method of inhibiting restenosis in a patient following balloon angioplasty comprising administering to the patient a therapeutically effective amount of an angiogenic thrombin derivative peptide which has angiogenic activity and comprises a thrombin binding domain and a serine esterase conserved sequence. Claim 21 is

directed to a stent coated with an angiogenic thrombin derivative peptide which has angiogenic activity and comprises a thrombin binding domain and a serine esterase conserved sequence.

Malinda *et al.*, Unger *et al.* and Carney *et al.* are discussed in detail above. Importantly, as discussed above, Unger *et al.* would not have led one of ordinary skill in the art "to expect that *any* angiogenic agent would work to promote cardiac cell growth and revascularization in accordance with the teachings of Malinda et al.". Additionally, Malinda *et al.*, Unger *et al.* and Carney *et al.*, either alone or in combination, do not teach or suggest that an angiogenic thrombin derivative peptide comprising a thrombin binding domain and a serine esterase conserved sequence can be used to inhibit restenosis with a reasonable expectation of success. In fact, Malinda *et al.* teach that the Tα1 peptide disclosed therein can induce angiogenesis and stimulate collateral circulation in cardiac tissue affected by coronary occlusion, thereby restoring blood flow to ischemic tissues. Unger *et al.* teach that growth promoting peptides disclosed therein can induce the growth of cardiac blood vessels to facilitate the growth of cardiac blood vessels in the heart. Inducing angiogenesis and stimulating growth of new blood vessels have nothing to do with inhibiting restenosis.

Moreover, contrary to the Examiner's contention, Saadat *et al.* do not teach or suggest the use of stents to relieve stenosis. Rather, Saadat *et al.* teach the use of stents for forming channels in the epicardium at a position ***adjacent*** to a stenosed cardiac artery (Col. 11, ll. 29-35). Bioreactive agents included on stents inserted in the epicardium are said to encourage revascularization, including the growth of new networks of capillaries that provide blood to the tissue downstream of stenosis (Col. 11, ll. 38-41). More generally, Saadat *et al.* teach stents that are used for forming channels in a wall of a vessel or organ and that may include a bioactive agent that stimulates revascularization and/or tissue growth (Col. 4, ll. 61-65). The bioactive agent is said to stimulate tissue regeneration and/or vascularization in tissue ***adjacent*** to the stent following implantation (Col. 3, ll 41-44). Accordingly, contrary to the Examiner's assertion, one of ordinary skill in the art would not have reasonably been led to expect that the bioactive agents of Saadat *et al.* "would by definition inhibit restenosis in the patient." As such, Saadat *et al.* do not cure the deficiencies of the Malinda *et al.*, Unger *et al.* and Carney *et al.* patents.

Accordingly, none of the cited references, alone or in combination, would have suggested the methods of Claims 12, 14 and 16-20 to one of ordinary skill in the art at the time of the

invention, with a reasonable expectation of success. None of the cited references, alone or in combination, would have suggested the stent of Claim 21 to one of ordinary skill in the art at the time of the invention, with a reasonable expectation of success. In particular, none of the cited references, either alone or in combination, would have suggested that an angiogenic thrombin derivative peptide comprising a thrombin binding domain and a serine esterase conserved sequence could be used to successfully inhibit restenosis. In fact, prior to Applicant's results described in the subject application (see Example 4), one of ordinary skill in the art would not have reasonably expected that angiogenic thrombin derivative peptide comprising a thrombin binding domain and serine esterase conserved sequence can successfully inhibit restenosis.

Reconsideration and withdrawal of this rejection of Claims 12, 14 and 16-21 under 35 U.S.C. § 103(a) are respectfully requested.

Item 10: Rejection of Claims 13 and 15 Under 35 U.S.C. § 103(a)

Claims 13 and 15 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Malinda *et al.* (U.S. Patent No. 6,197,751 B1) in view of Unger *et al.* (U.S. Patent No. 5,244,460), Carney *et al.* (U.S. Patent No. 5,352,664) and Saadat *et al.* (U.S. Patent No. 6,363,938 B2) and further in view of Nakahara *et al.* (U.S. Patent No. 6,191,113 B1). Malinda *et al.*, Unger *et al.*, Carney *et al.* and Saadat *et al* are applied as discussed above. In support of the rejection, the Examiner alleges that it would have been obvious to one of ordinary skill in the art "to coat the peptides of Carney et al. ('644) onto a balloon for administration with the expectation of achieving the benefits taught by Nakahara et al." (Paper No. 03022004, at page 9, fourth paragraph). Applicant respectfully disagrees that Claims 13 and 15 are obvious in view of the cited references.

Applicant notes that Claims 13 and 15 ultimately depend from Claim 1. For the reasons set forth above, Unger *et al.* would not have led one of ordinary skill in the art "to expect that *any* angiogenic agent would work to promote cardiac cell growth and revascularization in accordance with the teachings of Malinda et al.". Additionally, Malinda *et al.*, Unger *et al.*, Carney *et al.* and Saadat *et al.*, either alone or in combination, do not teach or suggest that an angiogenic thrombin derivative peptide comprising a thrombin binding domain and a serine esterase conserved sequence can be used to inhibit restenosis with a reasonable expectation of success.

Nakahara *et al.* teach specific peptides for use in inhibiting growth of smooth muscle cells, and in preventing or treating arteriosclerosis associated with growth of smooth muscle cells, restenosis after PTCA or other angioplasties, luminal stenosis after grafting blood vessels and smooth muscle sarcoma (Col. 3, ll. 53-62). Nakahara *et al.* teach that the TFPI peptide is administered directly into the lesion of a blood vessel via a drug delivery catheter, coated on the surface of a stent or balloon which is then administered to the lesion of the blood vessel or introduced into the vein or artery as a bolus or continuously (Col. 6, ll. 24-31). Nakahara *et al.* teach that their peptides comprise a peptide (A) of an amino acid sequence abundant in basic amino acid residues and a peptide (B) of an amino acid sequence comprising at least two consecutive, hydrophobic amino acid residues wherein the peptide (B) is linked to the C-terminal of the peptide (A) (Col. 4, ll. 22-28). Nakahara *et al.* disclose specific examples of their peptides, including tissue factor pathway inhibitor (TFPI) peptides, at Column 4, line 29 to column 5, line 17. The peptides disclosed by Nakahara *et al.* are not thrombin derivative peptides. Importantly, it is evident from the amino acid sequences disclosed by Nakahara *et al.* for their peptides that they do not comprise a thrombin binding domain and a serine esterase conserved sequence and therefore, are unrelated to the angiogenic thrombin derivative peptides recited in Applicant's claims. Since the peptides disclosed by Nakahrar *et al.* are not based on a thrombin sequence, one of ordinary skill in the art would not have been able to predict which thrombin fragments would be effective in inhibiting restenosis, based on the teachings of Nakahara *et al.* As such, Nakahara *et al.* do not teach or suggest that the angiogenic thombin derivative peptides recited in Claims 13 and 15 can be used to successfully inhibit restenosis. As such, Nakahara *et al.* do not cure the deficiencies of the Malinda *et al.*, Unger *et al.*, Carney *et al.* and Saadat *et al.* patents.

Accordingly, none of the cited references, alone or in combination, would have suggested the methods of Claims 13 and 15 to one of ordinary skill in the art at the time of the invention, with a reasonable expectation of success. In particular, none of the cited references, either alone or in combination, would have suggested that an angiogenic thrombin derivative peptide comprising a thrombin binding domain and a serine esterase conserved sequence could be used to successfully inhibit restenosis.

Reconsideration and withdrawal of this rejection of Claims 13 and 15 under 35 U.S.C. § 103(a) are respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

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